

We claim:

1. A monoclonal antibody or an antigen-binding portion thereof that specifically binds the capsular polysaccharide glucuronoxylomannan (GXM) of *Cryptococcus neoformans*, wherein said antibody or portion comprises:
  - (a) a heavy chain amino acid sequence comprising CDR1, CDR2 and CDR3 amino sequences of a human VH 3-64 gene or a human VH-6-1 gene, with or without a signal sequence;
  - (b) a light chain amino acid sequence comprising CDR1, CDR2 and CDR3 amino sequences of a human V $\kappa$  A27 gene, with or without a signal sequence; or
  - (c) both (a) and (b),wherein said amino acid sequence may comprise up to 6 mutations from the germline gene sequence.
2. The antibody or antigen binding portion according to claim 1, wherein the amino acid sequences are the germline gene sequences.
3. The antibody or antigen-binding portion according to claim 1, wherein the antibody comprises heavy chain and light chain CDR1, CDR2 and CDR3 sequences selected from the group consisting of:
  - (a) the heavy chain CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO: 43 and the light chain CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO: 1;
  - (b) the heavy chain CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO: 47 and the light chain CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO: 5; and
  - (c) the heavy chain CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO: 51 and the light chain CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO: 9.
4. The antibody or antigen-binding portion according to claim 1, wherein the antibody comprises a heavy chain and a light chain, and wherein the amino

acid sequences of the heavy chain and light chain are selected from the group consisting of:

(a) the amino acid sequence of the heavy chain and the amino acid sequence of the light chain of antibody G14F7E5, with or without signal sequences;

(b) the amino acid sequence of the heavy chain and the amino acid sequence of the light chain of antibody G15B4G5 with or without signal sequences; and

(c) the amino acid sequence of the heavy chain and the amino acid sequence of the light chain of antibody G19B9G7 with or without signal sequences.

5. The antibody or antigen-binding portion according to claim 1, wherein the heavy chain and the light chain comprise a heavy chain variable domain and a light chain variable domain, respectively, selected from the group consisting of:

(a) the heavy chain variable domain of SEQ ID NO: 43 and the light chain variable domain of SEQ ID NO: 1, with or without the signal sequence;

(b) the heavy chain variable domain of SEQ ID NO: 47 and the light chain variable domain of SEQ ID NO: 5, with or without the signal sequence; and

(c) the heavy chain variable domain of SEQ ID NO: 51 and the light chain variable domain of SEQ ID NO: 9, with or without the signal sequence.

6. A cell line selected from the group consisting of G14F7E5 (ATCC Accession No. PTA-5170), G15B4G5 (ATCC Accession No. PTA-5171) or G19B9G7 (ATCC Accession No. PTA-5172).

7. A monoclonal antibody produced by the cell line according to claim 6.

8. A monoclonal antibody that specifically binds *C. neoformans* GXM wherein the antibody comprises the heavy chain and light chain amino acid sequence of the monoclonal antibody according to claim 7.
- 5 9. An isolated antibody that specifically binds *C. neoformans* GXM, wherein the light chain of said antibody utilizes a human V<sub>κ</sub>III DPK22/A27 gene.
10. The antibody according to claim 6, wherein the light chain further utilizes a human J<sub>κ</sub>1 gene.
- 10 11. An isolated antibody that specifically binds *C. neoformans* GXM, wherein the heavy chain of said antibody utilizes a human V<sub>H</sub> 3-64 or a human V<sub>H</sub> 6-1 gene.
- 15 12. An antibody or an antigen-binding portion thereof that specifically binds the capsular polysaccharide glucuronoxylomannan (GXM) of *Cryptococcus neoformans*, wherein said antibody or portion comprises a light chain, said light chain amino acid sequence comprising an amino acid sequence selected from the group consisting of:
- 20 (a) the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 13;
- (b) the amino acid sequence of residues 1 to 99, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 13;
- (c) the amino acid sequence of residues 16 to 89, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID
- 25 NO: 13; and
- (d) the CDR1, CDR2 and CDR3 amino acid sequences encoded by the DNA sequences set forth in SEQ ID NOs: 14, 15 and 16.
- 30 13. A nucleic acid molecule comprising a nucleotide sequence encoding an amino acid sequence selected from the group consisting of:
- (a) the amino acid sequence set forth in SEQ ID NO: 1;

- (b) the amino acid sequence of residues 1 to 99, inclusive of the amino acid sequence set forth in SEQ ID NO: 1;
- (c) the amino acid sequence of residues 16 to 89, inclusive, of the amino acid sequence set forth in SEQ ID NO: 1; and
- 5 (d) the CDR1, CDR2 and CDR3 amino acid sequences set forth in SEQ ID NOs: 2, 3 and 4.
14. A polypeptide comprising an amino acid sequence selected from the group consisting of:
- 10 (a) the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 13;
- (b) the amino acid sequence of residues 1 to 99, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 13;
- (c) the amino acid sequence of residues 16 to 89, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID
- 15 NO: 13; and
- (d) the CDR1, CDR2 and CDR3 amino acid sequences encoded by the DNA sequences set forth in SEQ ID NOs: 14, 15 and 16.
- 20 15. A nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:
- (a) the sequence set forth in SEQ ID NO: 13;
- (b) the nucleotide sequence of positions 1 to 297 of SEQ ID NO: 13;
- (c) the CDR1-CDR3 encoding sequence of SEQ ID NO:13; and
- 25 (d) the CDR1, CDR2 and CDR3 encoding sequences of SEQ ID NOs: 14, 15 and 16.
16. An antibody or an antigen-binding fragment thereof that specifically binds the capsular polysaccharide glucuronoxylomannan (GXM) of *Cryptococcus neoformans*, wherein said antibody or fragment comprises a light chain comprising an amino acid sequence selected from the group consisting of:
- 30 (a) the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 17;

- (b) the amino acid sequence of residues 1 to 102, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 17;
- (c) the amino acid sequence of residues 19 to 92, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 17; and
- (d) the CDR1, CDR2 and CDR3 amino acid sequences encoded by the DNA sequences set forth in SEQ ID NOs: 18, 19 and 20.
17. A polypeptide comprising an amino acid sequence selected from the group consisting of:
- (a) the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 17;
- (b) the amino acid sequence of residues 1 to 102, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 17;
- (c) the amino acid sequence of residues 19 to 92, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 17; and
- (d) the CDR1, CDR2 and CDR3 amino acid sequences encoded by the DNA sequences set forth in SEQ ID NOs: 18, 19 and 20.
18. A nucleic acid molecule comprising a nucleotide sequence encoding an amino acid sequence selected from the group consisting of:
- (a) the amino acid sequence encoded set forth in SEQ ID NO: 5;
- (b) the amino acid sequence of residues 1 to 102, inclusive, of the amino acid sequence set forth in SEQ ID NO: 5;
- (c) the amino acid sequence of residues 19 to 92, inclusive, of the amino acid sequence set forth in SEQ ID NO: 5; and
- (d) the CDR1, CDR2 and CDR3 amino acid sequences set forth in SEQ ID NOs: 6, 7 and 8.
19. A nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

- (a) the DNA sequence set forth in SEQ ID NO: 17;  
(b) the nucleotide sequence of positions 1 to 306 of SEQ ID NO: 17;  
(c) the CDR1-CDR3 encoding DNA sequence of SEQ ID NO: 17; and  
(d) the CDR1, CDR2 and CDR3 encoding DNA sequences of SEQ ID  
5 NOs: 18, 19 and 20.

20. An antibody or an antigen-binding fragment thereof that specifically binds the capsular polysaccharide glucuronoxylomannan (GXM) of *Cryptococcus neoformans*, wherein said antibody or fragment comprises a light chain  
10 amino acid sequence comprising an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 21;  
(b) the amino acid sequence of residues 1 to 96, inclusive, of the amino  
15 acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 21;  
(c) the amino acid sequence of residues 13 to 86, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 21; and  
(d) the CDR1, CDR2 and CDR3 amino acid sequences encoded by the  
20 DNA sequences set forth in SEQ ID NOs: 22, 23 and 24.

21. A polypeptide comprising an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence encoded by the DNA sequence set forth in  
25 SEQ ID NO: 21;  
(b) the amino acid sequence of residues 1 to 96, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 21;  
(c) the amino acid sequence of residues 13 to 86, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID  
30 NO: 21; and  
(d) the CDR1, CDR2 and CDR3 amino acid sequences encoded by the DNA sequences set forth in SEQ ID NOs: 22, 23 and 24.

22. A nucleic acid molecule comprising a nucleotide sequence encoding an amino acid sequence selected from the group consisting of:
- (a) the amino acid sequence set forth in SEQ ID NO: 9;
  - (b) the amino acid sequence of residues 1 to 96, inclusive, of the amino acid sequence set forth in SEQ ID NO: 21;
  - (c) the amino acid sequence of residues 13 to 86, inclusive, of the amino acid sequence set forth in SEQ ID NO: 9; and
  - (d) the CDR1, CDR2 and CDR3 amino acid sequences set forth in SEQ ID NOs: 10, 11 and 12.
23. A nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:
- (a) the DNA sequence set forth in SEQ ID NO: 21;
  - (b) the nucleotide sequence of positions 1 to 288 of SEQ ID NO: 21;
  - (c) the CDR1-CDR3 encoding DNA sequence of SEQ ID NO: 21; and
  - (d) the CDR1, CDR2 and CDR3 encoding DNA sequences of SEQ ID NOs: 22, 23 and 24.
24. An antibody or an antigen-binding portion thereof that specifically binds the capsular polysaccharide glucuronoxylomannan (GXM) of *Cryptococcus neoformans*, wherein said antibody or portion comprises a light chain, said light chain amino acid sequence comprising an amino acid sequence selected from the group consisting of:
- (a) the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 31, 35 or 39;
  - (b) the amino acid sequence of residues 1 to 150, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 31; residues 1-136, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 35; or residues 1 to 146, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 39;
  - (c) the amino acid sequence of residues 50 to 139, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 31; the amino acid sequence of residues 40 to 125, inclusive, of the

amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 35; the amino acid sequence of residues 46 to 135, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 39; and

- 5 (d) the CDR1, CDR2 and CDR3 amino acid sequences encoded by the DNA sequences set forth in SEQ ID NOs: 32, 33 and 34; 36, 37 and 38 or 40, 41 and 42.

- 10 25. A nucleic acid molecule comprising a nucleotide sequence encoding an amino acid sequence selected from the group consisting of:
- (a) the amino acid sequence set forth in SEQ ID NO: 43, 47 or 51;
- (b) the amino acid sequence of residues 1 to 150, inclusive of the amino acid sequence set forth in SEQ ID NO: 43; residues 1-136, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID
- 15 NO: 35; or residues 1 to 146, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 39;
- (c) the amino acid sequence of residues 50 to 139, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 31; the amino acid sequence of residues 40 to 125, inclusive, of the
- 20 amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 35; the amino acid sequence of residues 46 to 135, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 39; and
- (d) the CDR1, CDR2 and CDR3 amino acid sequences encoded by the
- 25 DNA sequences set forth in SEQ ID NOs: 32, 33 and 34; 36, 37 and 38 or 40, 41 and 42.

26. A polypeptide comprising an amino acid sequence selected from the group consisting of:
- 30 (a) the amino acid sequence set forth in SEQ ID NO: 43, 47 or 51;
- (b) the amino acid sequence of residues 1 to 150, inclusive of the amino acid sequence set forth in SEQ ID NO: 43; residues 1-136, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID

NO: 35; or residues 1 to 146, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 39;

(c) the amino acid sequence of residues 50 to 139, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 31; the amino acid sequence of residues 40 to 125, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 35; the amino acid sequence of residues 46 to 135, inclusive; of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 39; and

(d) the CDR1, CDR2 and CDR3 amino acid sequences encoded by the DNA sequences set forth in SEQ ID NOs: 32, 33 and 34; 36, 37 and 38 or 40, 41 and 42.

27. The nucleic acid molecule according to any one of claims 13, 15, 18, 19, 22, 23 and 25, operably linked to an expression control sequence.

28. A host cell transformed with a nucleic acid molecule according to claim 27.

29. A method for producing an antibody or an antigen binding fragment thereof that specifically binds *C. neoformans* GXM, comprising the step of culturing a host cell according to claim 28.

30. A host cell transformed with a nucleic acid molecule according to any one of claims 13, 15, 18, 19, 22, 23 and 25.

31. A method for producing an antibody or an antigen binding fragment thereof that specifically binds *C. neoformans* GXM, comprising the step of culturing a host cell according to claim 30.

32. A composition comprising the antibody or antigen-binding fragment thereof according to any one of claims 1-5, 7-12, 16, 20 and 24, and a pharmaceutically acceptable carrier.

- 5
33. The composition according to claim 32, further comprising a component selected from the group consisting of:  
(a) a diagnostic agent; and  
(b) a therapeutic agent.
- 10
34. A kit comprising the antibody or antigen-binding fragment thereof according to any one of claims 1-5, 7-12, 16, 20 and 24.
35. A method for preventing or reducing the severity of conditions or disorders caused by *C. neoformans* infection in a subject in need thereof comprising the step of administering an effective amount of the antibody or antigen-binding fragment thereof according to any one of claims 1-5, 7-12, 16, 20 and 24 or a composition according to any one of claims 32 or 33.
- 15
36. A method for increasing the resistance of a subject in need thereof to infection by *C. neoformans* or to conditions or disorders caused by such infection, comprising the step of administering the antibody or antigen-binding fragment thereof according to any one of claims 1-5, 7-12, 16, 20 and 24 or a composition according to any one of claims 32 or 33.
- 20
37. The method according to claim 35 or 36, wherein the subject is immunocompromised.
- 25
38. The method according to claim 35 or 36, wherein the subject is infected with HIV-1.
39. The method according to claim 35 or 36 wherein the subject lacks one or more human V<sub>H</sub> 3 family genes.
- 30
40. The method according to any one of claims 35-39, wherein the anti-*C. neoformans* GXM antibody or antigen-binding fragment thereof is administered in conjunction with the administration of another therapeutic agent.

41. A method for detecting *C. neoformans* infection comprising contacting a sample from a subject suspected of being infected with an antibody or antigen-binding fragment according to any one of claims 1-5, 7-12, 16, 20 and 24 and detecting the binding of said antibody or fragment to *C. neoformans* GXM.

42. The antibody or antigen-binding portion according to any one of claims 1-5, 7-12, 16, 20 and 24 which is derived from a non-human transgenic animal.

43. The antibody or antigen-binding portion according to claim 42, wherein the non-human transgenic animal is a XenoMouse® animal.